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APPLICATION NUMBER:

761178Orig1s000

OTHER REVIEW(S)

BLA 761178 IMMUNOGENICITY REVIEW

Application Type	BLA
Application Number	761178
Submit Date	July 7, 2020 for Part 3 containing immunogenicity
Received Date	July 7, 2020
BsUFA Goal Date	June 7, 2021
Division/Office	Office of Neuroscience, Division of Neurology I
Review Completion Date	November 2, 2020 revised November 9, 2020 revised June 4, 2021
Product Code Name	
Proposed Proper Name¹	aducanumab
Proposed Proprietary Name¹	Aduhelm
Pharmacologic Class	Monoclonal antibody
Applicant	Biogen
Applicant Proposed Indication(s)	Delay clinical decline in early Alzheimer's disease (b) (4)
Recommended Regulatory Action	There are no immunogenicity issues to prevent approval

Immunogenicity Reviewers

Primary Reviewer(s)	Fred Mills
Secondary Reviewer(s)	Haoheng Yan

¹ The proposed proper and proprietary names are conditionally accepted until such time that the application is approved.

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1.1 Immunogenicity Executive Summary and Recommendation

Biogen has developed aducanumab, a monoclonal antibody with high affinity for aggregated forms of Ab-amyloid protein whose aggregation is thought to be an important aspect of the pathological processes in the brain that underlie development of Alzheimer's disease. This review consists of the OBP assessment of the immunogenicity data for the aducanumab clinical trials that have been submitted in BLA 761178 to support licensing. Overall the immunogenicity assessment is adequate.

The assay for Anti-Drug Antibodies (ADA) is a bridging ELISA, in which samples react in solution with biotin-aducanumab and DIG aducanumab to form a bridging complex between the two reagents and ADA. The complexes are then captured via the biotin moiety in streptavidin-coated of an ELISA plate, and bound complexes are detected with anti-DIG HRP. The ADA assay has a validated sensitivity of 15.625 ng /ml mouse monoclonal control antibody, well within the limit recommended in the 2019 FDA guidance for immunogenicity assays of 100 ng / ml. In addition to sensitivity, the ADA assay has been adequately validated for Low and High Positive controls, precision of screening, confirmatory, and titer assays, specificity, selectivity and matrix interference, robustness, and control reagent stability. The sponsor did not assess the effects of hemolysis and lipidemia, and subject to a pending IR response, these assessments are being considered as PMCs.

In the course of their clinical trials, the sponsor prepared and used 5 different lots of biotin-aducanumab and DIG-aducanumab detection reagents. This necessitated partial revalidation after incorporation of each set of reagents into the ADA assay. These partial re-validations were for NC, LPC/NC and HPC/NC system suitability limits and were adequate. In addition, it was necessary to re-validate the assay for Drug Tolerance (DT). For four of the detection reagent lots the DT determined at a level of 15.625 ng /ml positive control antibody was 31.25 µg/ml aducanumab or higher, which is higher than the expected range of trough drug concentrations, as per communication with Clinical Pharmacology. For one lot of detection reagents, the drug tolerance at 15.625 ng /ml positive control antibody was 15. 625 µg/ml aducanumab. However, in response to the 9/23/2020 IR regarding this issue, the sponsor clarified that only one clinical sample had a serum aducanumab above the DT at the 15.625 ng/ ml anti-aducanumab level, and no samples were above the DT for the 100 ng /ml level of anti-aducanumab control antibody, indicating that for practical purposes the DT of assay is adequate.

No NAb assay was developed or used in the aducanumab clinical trials. Biogen received agreement with FDA by email on February 12, 2018 their proposal to identify subjects with neutralizing anti-aducanumab antibodies by correlating anti-aducanumab antibody positivity to changes in aducanumab exposure and/or efficacy in treated subjects. However, in the BLA submission this approach was not feasible due to the low ADA incidence (discussed below). Therefore Biogen performed ad-hoc analysis across 5 studies for ADA effect on clearance, and concluded that the systemic exposures of aducanumab including AUC and Cavg for ADA positive individuals were not affected by the ADA. The need for a NAb assay was discussed with Clin-Pharm during the internal team meeting Oct 27, 2020. The Clin Pharm reviewer stated that he did not find a PMR for a NAb assay to necessary due to the low ADA incidence. OBP agreed with this recommendation.

Clinical immunogenicity results were obtained from the seven aducanumab clinical trials; i.e. Phase 1 (221AD101, 221AD103, 221AD104, 221HV102), Phase 2 ((221AD205), and Phase 3 studies (221AD301 and

221AD302). Overall low ADA incidence was observed in these studies: importantly in the parallel Phase 3 studies 221AD301 and 221AD 302 for subjects pooled across the placebo-controlled segments of the two trials the placebo group 9 of 1069 subjects (0.8%) were ADA positive with 0.2% treatment emergence, while for 1082 subjects receiving aducanumab there was a 1.9% positivity rate with 0.7% treatment emergent ADA. For data pooled across both the placebo controlled and LongTerm Extension (LTE) segments of these studies for subjects exposed to aducanumab there was low ADA incidence (1.4%) and low treatment emergent ADA (0.6%).

Across the other studies aducanumab there was low immunogenicity. In the earliest Phase 1 study 221AD101 there with 2 out of 39 (5%) aducanumab-treated positive for ADA and 2/14 (14%) placebo subjects being positive in treatment but also positive at baseline, while there were no positive immunogenicity samples observed in Phase 1 Studies 221AD104 and 221HV102, and in Phase 2 Study 221HV102

ADA incidence was somewhat higher for the Phase 1b study 221AD103, as 8 of 147 aducanumab-treated subjects (5%) had treatment-emergent anti-aducanumab antibodies with 2 of 47 (4%) in the placebo group. This higher incidence likely not due to inclusion of early time point samples as inspection of data shows that ADA positive sample were spread throughout the course of the trial. Nonetheless levels were still low in this 194 subject trial

Taken together, the ADA incidence for aducanumab trials was low. Therefore, aducanumab immunogenicity is not an important clinical concern.

1.2 Deficiencies and Other Recommended Comments to Applicant

PMC Language (12/07/2021 Final Report submission date accepted by Sponsor 5/25/21)

As discussed in the FDA 2019 guidance for immunogenicity assays, matrix effects arising from hemolysis and lipidemia have the potential to interfere with anti-drug antibody (ADA) assays. In this regard, there is an approximate 19% incidence of both hyperlipidemia and hypercholesterolemia in their Phase 3 studies (Summary Clinical Safety m.2.7.4), and these conditions make it more likely that there will be interfering lipids in ADA samples. Therefore the Sponsor should evaluate the potential for matrix interference from hemolysis and lipidemia in their assay for aducanumab ADA.

2. Review

Document Reviewed	Submission Date
BLA 761178 SN 03	July 7, 2020
BLA 761178 SN 27 responses to 9/23/2020 IR	September 30, 2020
BLA 761178 SN 48 responses to 10/26/2020 IR	November 2, 2020
BLA 761178 SN 78 responses 5/21/2021 IR	May 25, 2021

1.1 Immunogenicity Risk Assessment

There are no immunogenicity issues preventing approval.

1.2 Validation of Anti-Drug Antibody Assay

1.2.1 Method Principle

The ADA assay utilizes a bridging ELISA design. Samples or controls incubated in solution with a 1:1 mixture of biotin-aducanumab and DIG aducanumab, and reactive antibodies form a bridging complex between these two reagents. Solutions containing the bridging complexes are incubated ON in plates with streptavidin coated wells, so that the biotin moiety of the complexes binds to the streptavidin. After washing, the bound bridging complexes are detected using anti-DIG HRP.

1.2.2 Validation Exercises

Validation Parameter	Validation Report	Reviewer Comment
Contract Research Org	(b) (4)	Widely used contract testing firm for immunogenicity assays.
Assay principle	Bridging ELISA design. Samples or controls incubated in solution with a 1:1 mixture of biotin-aducanumab and DIG aducanumab, and reactive antibodies form a bridging complex between these two reagents. Solutions containing the bridging complexes are incubated ON in plates with streptavidin coated wells, so that the biotin moiety of the complexes binds to the streptavidin. After washing, the bound bridging complexes are detected using anti-DIG HRP.	<i>Bridging approach is standard for an ADA assay. In-solution formation of biotin-drug-ADA-DIG-drug complexes prior to binding to plate in theory may result in reduced background. Format is acceptable.</i>
Sample Pretreatment (Acid dissociation)	no	<i>Not necessary because the trough concentrations of Acunumab were in almost all cases less than the drug tolerance.</i>
Positive control (PC)	<i>Description below provided in response to 9/23/2020 IR</i> The aducanumab ADA positive control antibody is a purified monoclonal antibody (mouse IgG1 kappa) generated from a murine hybridoma cell line (b) (4). It is an anti-idiotypic antibody directed against the complementarity-determining region (CDR) of BIIB037 (aducanumab). Furthermore, it is characterized as a neutralizing anti-drug antibody that blocks the binding of BIIB037 to its target amyloid beta.	<i>Control not described in original submission. Description provided in response to IR sent 9/23/2020. Description is adequate</i>
PC Dose Curve and Hook Effect	no	<i>Not required as only low signals were observed in clinical studies</i>

LPC	10 ng / ml	<i>Appropriately low LPC, slightly lower than determined 15.625 ng / ml sensitivity</i>
HPC	150 ng / ml	<i>Acceptable HPC given the observed levels for clinical positive ADA samples.</i>
Matrix and NC	Samples in serum or NC (serum samples without control antibody or ADA) were diluted 1:25 in Blocker PBS-Casein, followed by addition of equal volume of a solution containing an equimolar mixture of Biotin-aducanumab and DIG- aducanumab. The final dilution of controls and samples was 1:50, which was the minimal required dilution (MRD) of the assay.	<i>Patient sera, sera with controls, sera for cutpoint validation, or NC sera are diluted 1:25 in buffer relevant to the assay. This procedure is acceptable as the buffer composition is dictated by the need to control assay background.</i>
MRD	1 / 50	<i>Within guidance</i>
NC system suitability range	The control ranges were dependent on the biotin-aducanumab / DIG-aducanumab lots used, and thus part of the partial validations for these detection reagents, as discussed below under NC, LPC/NC and HPC/NC system suitability limits. Limits were assigned as mean - /+ 3SD, or equivalent non-parametric limits if the distributions were not normal.	<i>Suitability limits derived from the partial validations spanned ranges of approximately 2 to 3 fold, with large separations between NC, LPC/ NC, and HPC /NC ranges, supporting the appropriateness of these controls. Moreover, the precision aspects of the partial validations showed modest variability, indicating that assays are well controlled.</i>
LPC /NC system suitability range		
HPC/NC system suitability range		
Screening cut- point (SCP) factor	The screening cutpoint (factor) ranged from 1.24 to 1.9834. When these SCPs were applied to untreated serum data sets, the empirical false positive values ranged from 7.5% to 10.4%	<i>The SCPs all generate similar empirical False Positive Rates (7.5% to 10.4%), indicating the screening assay appropriately generates an appreciable FPR, and thus is unlikely to miss true positive samples. The SCPs are appropriate.</i>
Confirmatory cut- point (CCP) Floating	The Confirmatory Cutpoint targeted a 1% FPR for all detection reagents, and ranged from 16.7% to 26.6% inhibition. Applying these CPPs to untreated serum data sets, the empirical false positive values ranged from 0.0% to 1.69%	<i>The ranges for CCPs were 16.7% to 26.6%, and thus required and approximate 25% or less inhibition to confirm a positive. The empirical FPR are the expected range (0-1.69%) for a CCP targeting a 1% FPR. The CCP is appropriate.</i>
Titer (precision)	Groups of 6 titer series were analyzed four times (4 runs) by 2 analysts. Dilutions of the HPC gave titers that in all cases were within -/+ 2 dilutions of target titer of 3200 (1600-6400). The original labeled drug lots 2015-037-3B/3T were used for this study.	<i>Titer precision meets specification and means titers for clinical samples with a similar ADA content are likely to vary by only 2 fold. I have examined the associate tabulated data and find agree with the sponsor's statements. The titer precision is acceptable.</i>

Assay Drug tolerance	<p>The Drug Tolerance is dependent on the lots of detection reagents, and thus part of assay partial re-validation. This is discussed more fully in the section following this table on parameters that were part of the partial re-validation.</p> <p>Importantly, at the sensitivity limit for the assay (15.625 ng / ml) the drug tolerance was > 31.25 µg/ ml, except for the 2015-037-50D/52D detection reagents, for which the drug tolerance was 15. 625 µg/ ml</p>	<p><i>For labeled drug lot 2015-037-50D/52D the drug tolerance is 15.625 µg / ml. This reagent was used in the 103, 301, and 302 studies, and the validated 15.625 µg/ ml drug tolerance may be below the mean aducanumab trough values observed in these studies, which are in the range 21-27 mg / L, or 21-27 µg/ ml IR sent.</i></p> <p><i>From Biogen's response to the 9/23/2020 IR, only one sample had a drug concentration above the 15.625 µg / ml DT for the 15. 625 ng / ml sensitivity of the assay. Moreover, all the samples had drug concentrations below the DT for a 100 ng / ml assay sensitivity. Therefore I agree that the Drug Tolerance is acceptable.</i></p>
Target tolerance	NA	
Sensitivity	15.625 ng / ml	<i>Relatively high sensitivity-well within guidance recommendation of ≤ 100 ng /ml</i>
<u>Screening Assay</u> Repeatability/Intra-assay variability	<p>NC %CV 1.6 to 14.1</p> <p>LPC %CV 1.1 to 8.4</p> <p>HPC %CV 2.1 to 5.9</p> <p>Normalized PC / NC</p> <p>0.9 to 8.5</p> <p>2.1 to 5.9</p>	<i>Modest % CV values well with 20% specification. I have examined the associate tabulated data and find the sponsor's statements are accurate. Variability is acceptable.</i>
<u>Screening Assay</u> Intermediate Precision (IP)/inter-assay variability	<p>NC %CV 8.1</p> <p>LPC %CV 9.6</p> <p>HPC %CV 8.6</p> <p>Normalized PC / NC</p> <p>7.3</p> <p>6.1</p>	<i>As above</i>
<u>Confirmatory Assay</u> Repeatability/Intra-assay variability	<p>LPC % CV 0.6 to 8.8</p> <p>HPC % CV 0.1 to 0.5</p>	<i>As above</i>
<u>Confirmatory Assay</u> Intermediate Precision (IP)/inter-assay variability	<p>LPC % CV of % inhibition 4.4</p> <p>HPC % CV of % inhibition 0.4</p>	<i>As above</i>
<u>Titration assay precision</u>	<p>Over the four acceptable validation runs, the target titer for HPC was 3200.</p> <p>All the titers were within one 2-fold dilution</p>	<i>Titer precision meets specification, and means titers for clinical samples with a similar ADA content are likely to vary by</i>

	of the target titer (100%), and met the target acceptance criteria	<i>only 2 fold. I have examined the associate tabulated data and agree with the sponsor's statements. The titer precision is acceptable.</i>
Selectivity and Matrix Interference	<p>Screening: 10 non-Japanese AD and 10 normal Japanese samples spiked at LPC and HPC levels. All gave signals consistent with those observed elsewhere in validation. Unspiked were below the SCP.</p> <p>Confirmatory: The two samples sets above gave inhibition > the 21.7 % CCP with the HCP, while unspiked samples were negative</p> <p>Titer: Samples sets as above all gave a mean titer value of 3200</p> <p>(b) (4) states that selectivity and no matrix effects were demonstrated.</p>	<p><i>Examination of report ts307-069 where these data are found shows that the (b) (4) statement for screening are correct. For Confirmatory, one unspiked Japanese sample gave a 20.6 % inhibition-while all the other unspiked samples gave low inhibition. All the LPC spiked samples gave inhibition \geq 48.5%, and all the HPC spiked samples gave inhibition \geq 92.5% when treated with 50 μg/ml aducanumab.</i></p> <p><i>For Titer, 15 out of 20 samples gave a titer of 3200, with the remaining 5 samples giving a titer of 1600.</i></p> <p><i>Therefore, overall I agree with (b) (4) conclusion that selectivity and lack of matrix effects are demonstrated in the ADA assay.</i></p>
Robustness	<p>Streptavidin plate blocking time Assessed variation in going 1, 2, 3 hours. 1.5, 1.6, 2.5 % CV (HPC) and 2.4, 1.1, 1.7 for the 3 times assessed in three runs</p> <p>Overnight incubation time of samples % CV (HPC) and % (LPC) for 16, 20, 24 minutes across three runs.</p> <p>Sample incubation on streptavidin coated plate 14.6, 13.6, 14.1 %CV (HPC) and 8.6, 8.3, 8.5 %CV (LPC) for 45, 60, 75 minutes across three runs. Modest increase (~ 25%) with incubation time</p> <p>Incubation of detection reagent 8.4, 8.7, 7.7 % CV (HPC) and 8.4, 8.7, 7.7 % CV for 45, 60, 75 minutes across three runs.</p> <p>Substrate incubation 6.3 5.3 5.8 %CV (HPC) and 6.2, 6.0, 6.1 % CV (LPC) for 15, 20, 25 minutes across three runs. Slight increase with incubation time.</p> <p>Time to reading the plate after addition of stop solution: 0.9, 1.2, 1.0 % CV (HPC) and 1.0, 0.50.7 % CV (LPC) for 2, 5, 10, 20, 30 min across 3 runs</p> <p>Effect of Plate Lots For standard conditions two different plate lots across 2 runs gave 5.1, 6.4 %CV (HPC) and 0.3, 2.2 % CV (LPC).</p> <p>Effect of Plate Lots</p>	<i>The robustness studies yielded modest changes for the ranges of 7 different parameters studied. Thus the assay should yield valid results over these ranges of conditions.</i>

	For standard conditions two different plate lots across 2 runs gave 5.1, 6.4 %CV (HPC) and 0.3, 2.2 % CV (LPC)	
Specificity	HPC and LPC gave signals consistent with those throughout validation while samples containing unrelated an BIB033 anti-idiotypic antibody at the same concentrations as the LPC and HPC gave signal less than the screening cutpoint.	<i>I have examined the tabulated specificity data and find that (b) (4) statement is accurate for all the stability tests.</i>
Stability	<p>Acceptance Criteria At least two of the three aliquots for each stability condition met the control range acceptance criteria at both the HPC and LPC levels. %CV between the replicate wells within each LPC and HPC set met the %CV ≤20% criterion. For all the stability tests below, (b) (4) states that all three aliquots met the acceptance criteria.</p> <p>By these criteria Freeze/Thaw Stability: Demonstrated up to 10 freeze/thaw cycles Bench Top Stability: Demonstrated up 23 hours and 55 minutes Refrigerator Stability (2 to 8°C) : Demonstrated up 13 days Short-term Stability (-15 to -30°C): Demonstrated up to one month.</p>	<i>I have examined the tabulated stability data and find that the (b) (4) statement is accurate for all the stability tests.</i>
Lipidemia	<p>From 221AD301: CSR 221AD301 \\cdsesub1\evsprod\BLA761178\0003\m2\27-clin-sum</p> <p>20.7% of subjects had hyperlipidemia</p>	<p><i>The effects of hemolysis and lipidemia were not assessed, IR sent 9/23/2020. In their response Biogen argue that hemolysis and lipidemia are not likely to impact a heterogeneous immunoassay format, such as is used for this ADA assay. They also state that they do not find literature references for interference by hemolysis or lipidemia on ADA assays.</i></p> <p><i>However, OBP experience is that these matrices do have some effect on ADA assays. Therefore, on 10/26/2020 OBP sent an IR asking Biogen to provide data on the prevalence of hemolysis and lipidemia in samples used for immunogenicity testing in the aducanumab clinical studies.</i></p>
Hemolysis		<i>As above</i>
ADA Assay Assessment	Suitable/Not suitable for Intended purpose	<i>The ADA assay is suitable for its intended purpose.</i>

Parameters dependent on detection reagent lots

Because 5 different labeled drug lots (2015-037-3B/3T, 2015-037-42B/43D, 2015-037-49B, 2015-037-50D/52B, and 2016-063-18/19) were used during clinical development partial assay revelation was performed for each of these lots, with screening cutpoint, confirmatory cutpoint, control system suitability ranges, and drug tolerance being evaluated during each partial validation.

NC, LPC/NC and HPC/NC system suitability limits

Data from partial validation runs for each labeled drug lot were used to calculate NC, LPC/NC, and HPC/ NC ratios. Outliers were excluded, and the data were assessed for normality. In most cases it was necessary to use a natural log transformation to approximate a normal distribution, and in some cases (particularly for the NC) if transformation did not yield a normal distribution a nonparametric approach was used to assess the 99.7% percentile (equivalent to 3xSD range for normal distributions) to set the NC ranges .

The assay acceptance limits were derived as follows:

1. Calculate the interim control ranges for non-robustness runs using the following rules:
 - Lower ranges: Mean +/- 3xStdev for HPC/NC, LPC/NC, and NC
 - Upper ranges: Mean +/- 3xStdev for HPC/NC, LPC/NC, and NC
2. Apply these ranges to the robustness runs and excluded any data points which did not meet the interim ranges calculated in Step 1.
3. Calculate the final system suitability ranges for all acceptable runs using the following criteria
 - Lower ranges: Mean - 3xStdev for HPC/NC, LPC/NC, and NC
 - Upper ranges: Mean + 3xStdev for HPC/NC, LPC/NC, and NC

Shown below are summary results for the suitability limits from the partial validations. Note that in most cases these limits were back-transformed to yield OD ratios.

Performance of Quality Control Samples		Lot: 2015-037-3B/3T	Lot: 2015-037-43B/43D	Lot: 2015-037-49B/49D		Lot: 2015-037-50D/52B	Lot: 2016-061-18/19
		(Final)	(Final)	(Interim)	(Final)	(Final)	(Final)
Ranges	NC Response	0.049-0.109	0.045-0.087	0.0450-0.0718	0.0448-0.0696	0.0444-0.129	0.0444-0.129
	LPC/NC	1.047-3.963	1.885-6.931	3.152-8.136	2.536-8.402	2.537-4.407	2.537-4.407
	HPC/NC	14.632-36.888	14.999-76.708	31.956-64.937	29.742-66.116	18.897-38.811	18.897-38.811

Reviewer comments

The re-validation for control acceptance ranges yielded 2-3 fold ranges for the acceptance criteria, which seem somewhat broad. However, examination of the actual tabulated data for validation exercises across runs, days, and operators indicates narrow ranges of control values, and thus tight control in actual practice.

Drug tolerance

For drug tolerance, 2x BIIB037 (aducanumab) stock samples were prepared by serially diluting BIIB037 2-fold in blank matrix (negative control human serum) at a final concentration of 2000, 1000, 500, 250, 125, 62.5, 31.25, 15.63 and 0.00 ng/ml. Stock samples containing 2x PC were prepared by serially diluting anti- BIIB037 PC antibody 2-fold in blank matrix with resulting 2x concentrations of PC at a final concentration of 1000, 500,

250, 125, 62.5, 31.25, 15.63 and 0.00 ng/mL. Equal volumes of each 2x BIIB037 stock sample and each 2x anti- BIIB037 PC stock sample were mixed in cluster tubes and pre-incubated at room temperature for at least 2 hours but not more than 3 hours to allow drug:PC complex formation. The samples were stored at -60 to -80°C for at least 24 hours prior to use in the screening assay.

From ts307-069vr-adden-2.pdf, Report Addendum No.2, Table 1

Labelled Drug Lot #	Lot: 2015-037-3B/3T	Lot: 2015-037-43B/43D	Lot: 2015-037-49B/49D	Lot: 2015-037-50D/52B	Lot: 2016-061-18/19*
Drug Tolerance	Anti-BIIB037 antibodies at concentrations 15.625 ng/mL or higher could be detected in the presence of free drug at concentrations up to 31.250 µg/mL. The corresponding molar ratio of drug (BIIB037) to anti-BIIB037 antibody in this case was 2000:1	Anti-BIIB037 antibodies at concentrations 15.625 ng/mL or higher could be detected in the presence of free drug at concentrations up to 125 µg/mL. The corresponding molar ratio of drug (BIIB037) to anti-BIIB037 antibody in this case was 8000:1	Anti-BIIB037 antibodies at concentrations 15.625 ng/mL or higher could be detected in the presence of free drug at concentrations up to 125 µg/mL. The corresponding molar ratio of drug (BIIB037) to anti-BIIB037 antibody in this case was 8000:1	anti-BIIB037 antibodies at concentrations of 15.625 ng/mL or higher could be detected in the presence of free drug at concentrations up to 15.625 µg/mL. The corresponding molar ratio of drug (BIIB037) to anti-BIIB037 antibody in this case was 1000:1	Anti-BIIB037 antibodies at concentrations 15.625 ng/mL or higher could be detected in the presence of free drug at concentrations up to 31.250 µg/mL. The corresponding molar ratio of drug (BIIB037) to anti-BIIB037 antibody in this case was 2000:1

*Labelled Reagent Lot: 2016-061-18/19 was bridged with against Lot: 2015-037-50D/52B. There were no separate cut point assessments performed for labelled reagent lot 2016-061-18/19

Reviewer comments

For labeled drug lot 2015-037-50D/52D the drug tolerance is 15.625 µg / ml. This reagent was used in the 103, 301, and 302 studies, and the validated 15.625 µg/ ml drug tolerance may be below the mean aducanumab trough values observed in these studies, which are in the range 21-27 mg / L, or 21-27 µg/ ml. In response to the 9/23/2020 IR regarding this issue, the sponsor clarified that only one clinical sample had a serum aducanumab above the DT at the 15.625 ng/ ml anti-aducanumab level, and no samples were above the DT for the 100 ng /ml level of anti-aducanumab control antibody, indicating that for practical purposes the DT of assay is adequate.

Screening and Confirmatory Cutpoints

The screening assay cut point for this assay was determined using the baseline samples from the 221AD103 study. In addition, a set of samples from commercial sources and representing healthy subjects of non-Japanese and Japanese ethnicity were evaluated during the cut point runs to evaluate the applicability of the derived cut points to broader population that includes Japanese subjects.

The table below is from Method Validation Report Addendum 1, p.611, Appendix 23

Table 83: Summary of Cut point for all the Labeled BIIB037 lots

Biotin Labeled Drug Lot	DIG Labeled Drug Lot	Plate Lot	HRP Lot	Confirmatory Drug	Statistical Memo	Cutpoint		Comments	Clinical Studies Supported
						SCP	CCP		
2015-037-3B	2015-037-3T	141821	2015-037-15A	2015-037-15D Lot: 3-FIN-1993	TS037-069VR-A_Appendix 14 Cut point Memo: 27Aug2019*	1.46	21.7% (1% FPR)	NA	221AD103
2015-037-43B	2015-037-43D	146056	2015-037-41B	2015-037-15D Lot: 3-FIN-1993	TS037-069VR_Appendix 14** TS037-069VR-A_Appendix 24** Cut point Memo: 18Oct2016	1.34	30.1% (0.1% FPR)	Original CCP	221HV102, 221AD104
2015-037-43B	2015-037-43D	146056	2015-037-41B	2015-037-15D Lot: 3-FIN-1993	TS037-069VR_Appendix 14 Cut point Memo: 01Aug2019*	1.34	26.6% (1% FPR)	Revised CCP	221AD103, 221AD301, 221AD302
2015-037-49B	2015-037-49D	151666 156052	2017-052-25	2015-037-41E Lot: 3-FIN-1993	TS037-069VR_Appendix 14** TS037-069VR-A_Appendix 24** Cut point Memo: 11Jul2018	1.24	23.8% (0.1% FPR)	Original CCP	NA
2015-037-49B	2015-037-49D	151666 156052	2017-052-25	2015-037-41E Lot: 3-FIN-1993	TS037-069VR-A_Appendix 14 Cut point Memo: 01Aug2019*	1.24	16.7% (1% FPR)	Revised CCP	221AD103, 221AD301, 221AD302
2015-037-52D	2015-037-50B	156052	2016-061-10	2016-061-12 Lot: AS1018/3-FIN-2511	TS037-069VR-A_Appendix 14 Cut point Memo: 24Mar2019*	1.9384	20.21% (1% FPR)	Revised CCP	221AD301, 221AD302
2016-061-18	2016-061-19	156156	2016-061-11	2016-061-12 Lot: AS1018	***	***	***	NA	221AD205

SCP: Screen Cutpoint

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n.b. 2016-061-18 / 2016-061-19 was bridged with 2015-037-52D / 2015-037-50B validation.

Additional information on screening and confirmatory cutpoint validation is provided in the table below

Biotin labeled drug lot	DIG labeled drug lot	Cutpoint samples	Transform confirmatory	SCP	Empirical FPR	CCP	Empirical FPR
2015-037-34B	2015-037-3T	196 baseline 221AD101 42 Japanese, 42 normal	Transform confirmatory	1.46	7.5%	21.7 % 1% FPR	0.0%
2015-037-42B	2015-037-42B	119 baseline 221AD401	Transform confirmatory	1.34 Per 2019 guidance	10.4%	26.6 % 1% FPR	1.26%
2015-037-49B	2015-037-49D	80 baseline 221AD301, 221AD302	Transform confirmatory	1.24 Per 2019 guidance	9.21 %	16.7% 1% FPR	1.69%
2015-037-52D	2015-037-50B	120 baseline 221AD301-2	No transformation	1.9834 Per 2019 guidance	10.0%	20.21% 1% FPR	0.93%
2016-061-18	2016-061-19	Bridged with 2015-037-52D / 2015-37-50B					

Reviewer comments

The screening and confirmatory cutpoints were appropriately re-validated for each set of detection reagents, Except for the first set of detection reagents, the cutpoints were validated consistent with the FDA 2019 guidance for immunogenicity assays. The SCPs yielded empirical False Positive Rates ranging from 7.5% to 10.0%, demonstrating that these SCPs are not likely to miss true positives, but rather will actually yield a level of false positives consistently higher than the suggested 5% FPR. The Confirmatory CutPoints all require an appreciable level of inhibition (16.7%-26.6%), which is expected to confirm true positives, but does not require inhibition so great (> 50%) that the confirmatory assay would miss may low affinity antibodies. ..

Neutralizing Antibody Assay

A Nab assay was not developed or used in the aducanumab clinical trials.

Regarding the NAb assay, as per Biogen's response to the 9/23/ 2020 OBP IR

Biogen had previously proposed to FDA to monitor anti-aducanumab antibodies and aducanumab exposure data in an integrated fashion to inform on neutralizing activity based on the aducanumab immunogenicity risk assessment (submitted to IND 106230 on August 3, 2017, Serial No. 0239). Biogen received agreement with FDA (by email on February 12, 2018) on the above proposal to identify subjects with neutralizing anti-aducanumab antibodies by correlating anti-aducanumab antibody positivity to changes in aducanumab exposure and/or efficacy in treated subjects.

However, due to the low ADA incidence, this approach was not feasible. Biogen did perform an ad-hoc analysis across 5 studies for ADA effect on clearance, and concluded that the systemic exposures of aducanumab including AUC and Cavg for ADA positive individuals were not affected by the presence of anti-aducanumab antibodies.

Reviewer comments

The need for a NAb assay was discussed with Clin-Pharm during the internal team meeting Oct 27, 2020. The Clin Pharm reviewer stated that he did not find a PMR for a NAb assay to necessary due to the low ADA incidence. OBP agreed with this approach.

1.3 Clinical Immunogenicity Results

From the Integrated Summary of Immunogenicity

For all four Phase 1 studies (221AD101, 221AD103, 221AD104, 221HV102) baseline samples were collected followed by a collection at between 2 to 4 weeks to monitor the anticipated onset of early immunogenicity responses. For the Phase 2 (221AD205) and Phase 3 studies (221AD301 and 221AD302) only long term (2ndary) responses were captured, with post-baseline immunogenicity samples beginning at week 16 for Phase 2, and 24 weeks for Phase 3. In all studies subsequent the immunogenicity assessments were then spaced with a maximum of 8 weeks separation to establish persistence or response through year 2 of treatment. A similar approach was utilized for placebo cohorts that crossed over to drug treatment arms. For long-term extensions, the length between sampling was increased. In general, drug concentration assessments were collected at the same visits anti-aducanumab antibody samples to monitor impact on of immunogenicity on drug exposure.

Specific criteria used to characterize immunogenicity for 221AD205, 221AD301, and 221AD302 were as follows:

1. Subjects who screened positive for anti-aducanumab antibody at any point of the study were considered anti-aducanumab antibody positive.
2. Positive anti-aducanumab antibody responses were defined as treatment emergent if the participant had negative antibody evaluation at baseline or if the participant had an antibody positive evaluation at baseline but the postbaseline response was more than 2-fold increase in titer compared to the baseline response.
3. Subjects with treatment-emergent positive anti-aducanumab antibody responses were classified as persistent positive if a positive evaluation occurred ≥ 112 days (16 weeks) apart or a positive evaluation occurred at the last available time point with no further negative results available. Responses were classified as transient positive if only a single positive evaluation occurred (that was not the last assessment), or if more than 1 positive evaluation occurred within < 112 days (16 weeks) and not thereafter from the first positive evaluation.

Reviewer comments

The ADA characterization criteria is acceptable.

Study 221AD101

No subjects were positive for anti-aducanumab antibodies that were related to aducanumab treatment. Two aducanumab-treated subjects (2/39 [5%]), both in the 3.0 mg/kg dose group, and 2 subjects (2/14 [14%]) in the placebo group were anti-aducanumab antibody positive but were also positive at baseline. The titers of anti-aducanumab antibodies in positive subject samples were low within 1 or 2 dilutions from the detection limit and remained stable over time within acceptable ± 2 -fold variability of titers

Reviewer comments

Qualitatively, these results suggest that aducanumab is not highly immunogenic, but the small size of this study makes it difficult to draw strong conclusions.

Study 221AD103Placebo-Controlled Period

During the placebo-controlled period, 8 of 147 aducanumab-treated subjects (5%) had treatment-emergent anti-aducanumab antibodies; 2 of 47 (4%) in the placebo group, 2 of 30 (7%) in the 1 mg/kg group, 0 of 32 (0%) in the 3 mg/kg group, 3 of 30 (10%) in the 6 mg/kg group, 1 of 32 (3%) in the 10 mg/kg group, 2 of 23 (9%) in the 3 to 6 mg/kg titration group

Reviewer comments

Examination of the tabulated data for this placebo-controlled period shows that a similar number of positives occurred at immunogenicity sampling time-points throughout this study, indicating that the increased percentage of positives in this study do not result from the fact that samples were obtained at 4 and 8 weeks, versus taking the first samples only at 16 weeks or 24 weeks in the Phase 2 and Phase 3 studies. Nonetheless ADA levels were still low in this 194 subject trial, supporting the modest immunogenicity of aducanumab.

Active Treatment Period

For the purpose of defining treatment-emergent anti-aducanumab antibodies during the active treatment period, the baseline of the placebo-controlled period was used as baseline for early starters, and baseline of the LTE period (beginning of aducanumab treatment) was used as baseline for late starters (*placebo-treated subjects who transitioned to aducanumab at the start of the Long Term Extension*). During the active treatment period, a total of 16 of 184 subjects (9%) had treatment-emergent anti-aducanumab antibodies; 4 of 30 (13%) in the 1 to 3 mg/kg titration group, 0 of 42 (0%) in the 3 mg/kg group, 3 of 30 (10%) in the 6 mg/kg group, 2 of 32 (6%) in the 10 mg/kg group, 3 of 19 (16%) in the 3 to 6 mg/kg titration, and 4 of 31 (13%) in the 1 to 3 to 6 to 10 mg/kg titration group.

Reviewer comments

The number of positives continued to increase in the LTE, supporting the view that positives in this study are not a function of sampling at 4 and 8 weeks in the placebo-controlled segment.

Study 221AD104

There were no positive immunogenicity samples reported in this study.

Study 221HV102

There were no positive immunogenicity samples reported in this study.

Study 221AD205

There were no positive immunogenicity samples reported in this study.

Studies 221AD301 and 221AD302

For immunogenicity analysis, data from the Phase 3 Studies 301 and 302 were pooled because they were identically designed, the results were similar, and comprise the most robust dataset for evaluation of the immunogenicity of aducanumab. Both studies were conducted in a large number of subjects with mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia, and tested the proposed commercial dose of aducanumab (10 mg/kg after titration over 24 weeks), given IV once every 4 weeks

Pool A1 (Phase 3 Placebo-Controlled Pool)

This pool includes all randomized subjects who received at least 1 dose of study treatment (placebo or aducanumab) in the placebo-controlled period of the Phase 3 studies and allows for a direct comparison between aducanumab and placebo during the randomized placebo-controlled period of the Phase 3 studies.

In Pool A1, a total of 9 of 1069 subjects in the placebo group (0.8%) and 30 of 2151 subjects in the total aducanumab group (1.4%) were positive for anti-aducanumab antibodies at any time during the placebo-controlled period, including the pre-dose baseline. The majority of the positive responses occurred at baseline prior to the first dose. In the placebo group, 2 of 1069 subjects (0.2%) had treatment-emergent antibody responses, of which 1 participant had a persistent response and 1 participant had a transient response. In the total aducanumab group, 10 of 2151 subjects (0.5%) had treatment-emergent antibody responses. Of these 10 subjects, 2 subjects had a persistent response and 8 subjects had a transient response

Reviewer comments

In the A1 pool, for data from subjects in the placebo-controlled segment of the Phase 3 trial, a total of 9 of 1069 subjects in the placebo group (0.8%) were ADA positive. There were $2151 - 1069 = 1082$ subject receiving aducanumab, and of these $30 - 9 = 21$ positives, for a 1.9% positivity rate. In the placebo group, 2 of 1069 subjects (0.2%) had treatment-emergent antibody responses, of which 1 participant had a persistent response and 1 participant had a transient response. For subjects receiving aducanumab, $(10 - 2) / 1082 = 0.7\%$ had treatment emergent ADA, with 1 subject showing a persistent response and 7 subjects showing a transient response. Taken together, these data indicate modest immunogenicity for aducanumab.

Pool A2 (Phase 3 Aducantumab-Treated Pool)

This pool includes all randomized subjects who received at least 1 dose of aducanumab at any time in the Phase 3 studies, including placebo-controlled and/or LTE (Long Term Extension) periods, assessment of the overall immunogenicity profile including impact of longer term exposure based on all subjects exposed to aducanumab for the period of aducanumab treatment in the Phase 3 studies.

In Pool A2, 37 of 2689 subjects (1.4%) were positive for anti-aducanumab antibodies at any time during the aducanumab-treated period of the study, including the predose baseline visit. Of these, 15 subjects were treatment emergent (0.6%), with 9 subjects having transient responses and 6 subjects having persistent responses.

Reviewer comments

In this pool, for which the totality of Phase 3 aducanumab exposure was assessed, there was low ADA incidence (1.4%) and low treatment emergent ADA (0.6%) again supporting the view that aducanumab elicits only modest immunogenicity.

Information Requests Sent During Review

Sept 23, 2020 IR

FDA Information Request 1

Provide a complete description of the positive control antibodies used in the ADA assay.

FDA Information Request 2

Lipid or lysed RBC in serum samples often affect the measurement of ADA. Therefore, provide data for the effects of lipidemia and hemolysis on your ADA assay.

FDA Information Request 3

The efficacy of aducanumab therapy for AD may be reduced by neutralizing activity (NAb) of ADA and assessment of NAb activity may be important for patient management. Therefore, provide an adequate rationale for not having a NAb assay.

FDA Information Request 4

You have changed lots of labeled drug detection reagents during clinical development, necessitating partial assay re-validation, including determination of drug tolerance. For labeled drug lot 2015-037-50D/52D you have determined a drug tolerance of 15.625 µg / ml (ADA validation Report Addendum No.2, Table I). This reagent was used in your 103, 301, and 302 studies, and the validated 15.625 µg/ml drug tolerance may be below the mean aducanumab trough values observed in these studies, which are in the range 21-27 mg / L, or 21-27 µg/ ml. Therefore, in order to allow assessment of the accuracy of your ADA results, for each serum sample for which ADA were determined in 103, 301, and 302, provide the labeled drug lot, drug tolerance, ADA results, and aducanumab level at the time of sampling, highlighting samples for which the aducanumab levels were higher than the drug tolerance.

Biogen Response, received October, 2020Summary of Biogen responsesRequest 1'

An adequate description of the monoclonal antibody positive control was provided and is discussed in the Validation Exercises section of this review.

Request 2

In their response Biogen argued that hemolysis and lipidemia are unlikely to affect ADA assays for biologics, and that there is no published reference indicate interference from these factors.

Request 3

Biogen provided background on discussion with the FDA regarding the NAB assay, including agreement not to pursue NAb assay development as discussed in the NAb assay section of this review.

Request 4

Biogen provided adequate rationale for the suitability of Drug Tolerance for the ADA assay, and this is discussed in the Validation Exercises and Drug Tolerance sections of this review.

October 26, 2020 IR

To assist in our evaluation of potential impact on your ADA assay resulting from hemolysis and lipidemia, provide data on the frequency of hemolysis and lipidemia in serum samples obtained for immunogenicity testing in your studies.

Biogen Response, received Nov 2, 2020

As the identification of hemolytic and lipemic samples is not a routine assessment for immunogenicity analysis (i.e. not specified in the lab method or sample analysis plan), no formal determination of the frequency of hemolysis and lipidemia in serum samples was conducted by the test facility during immunogenicity sample analysis.

As previously indicated in Biogen's response to a recent FDA information request, submitted on September 30, 2020 (Sequence No. 0027), there is no scientific rationale to support that these

matrix anomalies would interfere in the ADA assay. Based on the evaluation of drug modality, drug target, disease population and ADA assay format there is no expectation that hemolysis or lipemia would interfere with the detection of anti-drug antibodies. For the full explanation please refer to the [Biogen Response](#) to FDA Information Request 2, submitted on September 30, 2020.

Reviewer comments

Biogen's response essentially repeats the arguments in their responses to the FDA's 9/23/2020 IR. It is the experience of OBP that assessment of matrix effects arising from hemolysis and lipidemia is typically part of ADA assay validation and examples of interference have been observed in several applications. In addition the potential interference from free hemoglobin and lipid is discussed in the FDA's 2019 guidance for development of immunogenicity assays. Finally, in the Aducanumab trials, there was an approximate 19% incidence of both hyperlipidemia and hypercholesterolemia in the Phase 3 studies (Summary Clinical Safety m.2.7.4), and these conditions make it more likely that there will be interfering lipids in ADA samples. Therefore I recommend a PMC for evaluating the potential for matrix interference from hemolysis and lipidemia.

IR sent 5/21/21

PMC Language

As discussed in the FDA 2019 guidance for immunogenicity assays, matrix effects arising from hemolysis and lipidemia have the potential to interfere with anti-drug antibody (ADA) assays. In this regard, there is an approximate 19% incidence of both hyperlipidemia and hypercholesterolemia in their Phase 3 studies (Summary Clinical Safety m.2.7.4), and these conditions make it more likely that there will be interfering lipids in ADA samples. Therefore the Sponsor should evaluate the potential for matrix interference from hemolysis and lipidemia in their assay for aducanumab ADA.

Biogen response 5/25/21

Biogen agreed to the FDA proposed 12/07/2021 submission data for the PMC final report

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/s/

FREDERICK C MILLS
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: June 1, 2021

To: Kevin Krudys, Clinical Reviewer
Division of Neurology Products (DN1)

E. Andrew Papanastasiou, Regulatory Project Manager, (DN1)

Tracy Peters, Associate Director for Labeling, (DN1)

From: Sapna Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for ADUHELM™ (aducanumab-avwa),
injection for intravenous use

BLA: 761178

In response to DN1's consult request dated July 15, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original BLA submission for ADUHELM™ (aducanumab-avwa) injection for intravenous use.

PI: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN1 (E. Andrew Papanastasiou) on May 19, 2021, and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on May 26, 2021.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room October 30, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Sapna Shah at (240) 402-6068 or Sapna.Shah@fda.hhs.gov.

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/s/

SAPNA P SHAH
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 26, 2021

To: E. Andrew Papanastasiou,
Regulatory Project Manager, RPM
Division of Neurology 1 (DN 1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Sapna Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ADUHELM (aducanumab)

Dosage Form and Route: injection, for infusion

Application Type/Number: BLA 761178

Applicant: Biogen Inc.

1 INTRODUCTION

On February 20, 2020, May 15, 2020, and July 7, 2020, Biogen Inc. submitted for the Agency's review a rolling submission of an Original New Biologic Drug Licensing Application (BLA) for ADUHELM (aducanumab) injection, for intravenous use. The purpose of the application is to seek approval for the use of ADUHELM (aducanumab) injection, for intravenous use to delay the clinical decline of patients with Alzheimer's disease. On January 27, 2021, Biogen submitted additional information which constituted a major amendment to the application. Therefore, the Agency extended the goal date by three months to provide time for a full review of the submission.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology 1 (DN 1) on July 15, 2020, for DMPP and OPDP respectively to review the Applicant's proposed MG for ADUHELM (aducanumab) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft ADUHELM (aducanumab) MG received on July 7, 2020 and received by DMPP and OPDP on May 19, 2021.
- Draft ADUHELM (aducanumab) Prescribing Information (PI) received on July 7, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 19, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008, the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHARON W WILLIAMS
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LASHAWN M GRIFFITHS
05/26/2021 01:06:16 PM

Clinical Inspection Summary

Date	2/8/2021
From	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Emilios (Andrew) Papanastasiou, Regulatory Project Manager Kevin Krudys, M.D., Medical Officer Ranjit Mani, M.D., Team Leader Division of Neurology 1 Office of Neuroscience
BLA #	761178
Applicant	Biogen
Drug	Aducanumab
NME	Yes
Proposed Indication	To delay clinical decline in patients with Alzheimer's disease
Consultation Request Date	7/28/2020
Summary Goal Date	11/18/2020, extended to 2/5/2021
Priority/Standard Review	Priority
PDUFA Date	3/7/2021, extended to 6/7/2021 due to major amendment

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigators (CIs) Drs. Ott and Van Dyck, and the sponsor, Biogen, were inspected in support of this BLA, covering Protocols 221AD103 and 221AD302. No significant GCP issues were discovered during the CI inspections. Although there were some findings during the sponsor inspection, as described below, the studies appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

On March 21, 2019, the sponsor announced the termination of two identical Phase 3 studies (221AD301 and 221AD302) based on the results of an interim futility analysis for data collected up to 12/26/2018. The sponsor performed subsequent efficacy analyses based on data available through March 20, 2019, with results that questioned the earlier assessment of futility. In analyses that included the data up to study termination, Protocol 221AD302 appeared to provide evidence of efficacy, though Protocol 221AD301 reportedly did not (and was therefore not covered during these inspections). Protocol 221AD302 was unblinded on 4/18/2019. During the sponsor inspection, one focus was to identify any changes made to data after unblinding of the study.

For Protocol 221AD302, clinical outcome assessments (COAs) were entered directly into an electronic device, the Virgil Tablet, provided by the vendor, MedAvante. COAs included the primary efficacy measure, i.e., the Clinical Dementia Rating (CDR) scale. During the sponsor inspection, changes to Week 78 CDR scores after study unblinding for visits occurring before study termination were identified for ten (<1%) subjects. These changes were made after review of data and query by MedAvante and subsequent discussion and concurrence by the blinded CDR rater. The changes occurred in the aducanumab low dose and high dose groups and included both increases and decreases in CDR scores.

A review of the Virgil Tablet Activity log noted instances of significant delays between the start and end dates of CDR assessments as well as delays between the end of the CDR assessment and the electronic signature. Once an electronic signature was completed, data could no longer be altered on the tablet, and the data was then uploaded into the database (Virgil Portal). Audit trails began when the data had been uploaded to the Virgil Portal. However, prior to the electronic signature, data could be changed on the Virgil Tablet without an audit trail record. A >8 hour delay between the start and end of Week 78 CDR assessments was noted for 3.8% of subjects for data collected prior to study termination. A >1 hour delay between the end of the CDR assessment and electronic signature was noted for 7.2% of Week 78 CDR assessments for data collected prior to study termination.

These time delays occurred throughout the study and were not identified until April 2019, after study termination, when the Virgil Activity Log report was provided to the sponsor upon request. Therefore, since these time delays were not identified during the conduct of the trial, there were no systems in place to alert the rater, clinical site, vendor, or sponsor in real time to prevent the delays. User Acceptance Testing (UAT), conducted by the sponsor, may have identified these issues so that they could have been addressed by the vendor prior to initiation of Protocol 221AD302. Since no audit trails were available until data was uploaded to the Virgil Portal, it is not known if there were any changes to data during these time delays. This information was provided to the FDA statistical reviewer, who performed sensitivity analyses excluding subjects with these time delays. These sensitivity analyses reportedly supported the overall efficacy conclusions for Protocol 221AD302.

II. BACKGROUND

Aducanumab intravenous injection is being developed under BLA 761178 (IND 106230) to delay clinical decline in patients with Alzheimer's disease. Aducanumab is a human immunoglobulin gamma 1 (IgG1) anti-amyloid beta (A β) monoclonal antibody that targets aggregated soluble and insoluble forms of A β . Aducanumab is hypothesized to delay clinical decline by removing amyloid plaques that accumulate in the brains of people with Alzheimer's disease.

On March 21, 2019, the sponsor announced the termination of two Phase 3 studies (221AD301 and 221AD302) based on the results of an interim futility analysis for data collected up to 12/26/2018. The sponsor performed subsequent efficacy analyses based on data available through March 20, 2019 with results that questioned the earlier assessment of futility. The sponsor and the review division held meetings to discuss these analyses, details of which are beyond the scope of this Clinical Inspection Summary (CIS).

The sponsor submitted the results of a Phase 3 study (Protocol 221AD302) and a Phase 1 study (Protocol 221AD103) to support the efficacy and safety of aducanumab to delay clinical decline in patients with Alzheimer's disease. The results of the Phase 3 Protocol 221AD301, which did not demonstrate efficacy, was also included in the BLA submission. Clinical investigator and sponsor inspections covered Protocols 221AD302 and 221AD103 only. Protocol 221AD301 was covered in a sponsor surveillance inspection conducted by the Medicines and Healthcare products Regulatory Agency (MHRA) and is briefly summarized in this CIS.

Protocol 221AD302

Title: "A Phase 3 multicenter, randomized, double-blind, placebo controlled, parallel-group study to evaluate the efficacy and safety of aducanumab (BIIB037) in subjects with early Alzheimer's disease"

Subjects: 1643 randomized

Sites: 181 sites in the following geographic areas: North America [71 sites (United States 58, Canada 13)], Asia/Pacific (27 sites), Western Europe (69 sites), and Eastern Europe (14 sites)

Study Initiation and Completion Dates: 9/15/2015 to 8/5/2019

This was a randomized, double-blind, placebo-controlled Phase 3 study in subjects with early Alzheimer's disease (AD). Included were male or female subjects, 50 to 85 years of age (inclusive), mild cognitive impairment (MCI) due to AD or mild AD, positive amyloid PET scan, consent to ApoE ε4 genotyping, and having one informant/caregiver who can provide accurate information about the subject's cognitive and functional abilities.

The subject must have met all of the following clinical criteria for MCI due to AD or mild AD:

- A Clinical Dementia Rating (CDR) global score of 0.5
- A Repeatable Battery for Assessment of Neuropsychological Status (RBANS) score of ≤ 85 of objective cognitive impairment (based on the Delayed Memory Index score)
- Mini-Mental State Examination (MMSE) score between 24 and 30 (inclusive)

Concomitant chronic medications were allowed if the doses had been stable for 4 weeks prior to Screening Visit 1 and during Screening up to Study Day 1. However, concomitant medications for AD (e.g., donepezil, rivastigmine, galantamine, tacrine, and memantine) were only allowed if the dose had been stable for 8 weeks prior to Screening Visit 1 and during Screening up to Study Day 1.

The protocol was comprised of four phases:

Screening: 8 weeks

Placebo-controlled Phase: 76 weeks

Investigational product (IP) was administered by IV infusion approximately every 4 weeks, over approximately 76 weeks, for a total of 20 doses. Randomization was stratified by site and ApoE ϵ 4 status. Based upon their ApoE ϵ 4 carrier status, subjects were randomized (1:1:1) to one of three groups:

ApoE ϵ 4 Carrier

- Aducanumab 3 mg/kg (low dose); 1 mg/kg for 2 doses, 3 mg/kg thereafter
- Aducanumab 10 mg/kg (high dose); 1 mg/kg for 2 doses, 3 mg/kg for 2 doses, 6 mg/kg for 2 doses, 10 mg/kg thereafter
- Placebo

ApoE ϵ 4 Non-Carrier

- Aducanumab 6 mg/kg (low dose); 1 mg/kg for 2 doses, 3 mg/kg for 4 doses, 6 mg/kg thereafter
- Aducanumab 10 mg/kg (high dose); 1 mg/kg for 2 doses, 3 mg/kg for 2 doses, 6 mg/kg for 2 doses, 10 mg/kg thereafter
- Placebo

Of note, as of Protocol Version 4 (3/24/2017), the high dose for the ApoE ϵ 4 carriers was changed from 6 mg/kg to 10 mg/kg. ApoE ϵ 4 carriers who were randomly assigned to the high-dose group when the target dose was 6 mg/kg must have received 2 doses or more at 6 mg/kg prior to being titrated up to 10 mg/kg.

Long-Term Extension Phase: up to 5 years per protocol

Subjects must have completed the placebo-controlled phase of the study, taken at least 14 doses of IP, and not missed more than 4 consecutive doses of IP.

Subjects who received aducanumab in the placebo-controlled phase continued to receive the same dose. Subjects randomized to placebo in the placebo-controlled phase were randomized (1:1) to receive dose-blinded aducanumab at the low or high dose administered as in the placebo-controlled phase (e.g. titration regimens, ApoE ϵ 4 status).

Follow-Up Safety Visit

This visit occurred at Week 94 for subjects who did not enter the Long-Term Extension Phase or 18 weeks after last administration of IP for subjects who withdrew from the study. A follow-up safety visit also occurred for subjects in the Long-Term Extension phase.

The ***primary efficacy endpoint*** was the change from baseline in CDR-SB score at Week 78.

Protocol 221AD103

Title: “A randomized, double-blinded, placebo-controlled multiple dose study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of BIIB037 [aducanumab] in subjects with prodromal or mild Alzheimer’s Disease”

Subjects: 197

Sites: 27 sites in the United States

Study Initiation and Completion Dates: 10/5/2012 to 7/31/2019

This was a Phase 1, randomized, double-blind, placebo-controlled study in subjects with prodromal or mild Alzheimer’s Disease (AD). Included were males or females, 50 to 90 years of age, positive 18F-AV-45 PET scan, consent for ApoE ε4 genotyping, a reliable informant or caregiver, and meeting criteria for prodromal or mild Alzheimer’s disease. Concomitant medications for AD were allowed if the doses were stable for 4 weeks prior to screening and throughout the study.

Subjects must have met all of the following criteria for ***Prodromal Alzheimer’s disease:***

- MMSE score between 24 and 30 (inclusive)
- A spontaneous memory complaint
- Objective memory loss, defined as a free recall score of ≤ 27 on the Free and Cued Selective Reminding Test (FCSRT)
- A global CDR score of 0.5
- Absence of significant levels of impairment in other cognitive domains
- Essentially preserved activities of daily living and an absence of dementia

Subjects must have met all of the following criteria for ***Mild Alzheimer’s disease:***

- MMSE scores between 20 and 26 (inclusive)
- A global CDR score of 0.5 or 1.0
- Meeting the National Institute on Aging-Alzheimer’s Association core clinical criteria for probable Alzheimer’s disease

The study was comprised of four periods:

Screening Period – up to 60 days**Placebo-Controlled Period:** 12 months

The placebo-controlled phase was a staggered, parallel-group design with the first 3 treatment arms (Arms 1 to 3) enrolled in parallel, followed by Arms 4 and 5 enrolled in parallel, etc. Dose escalation was based on independent Data Monitoring Committee recommendations following review of data.

Subjects received 14 doses of investigational product (IP) administered by intravenous infusion every 4 weeks:

- Arms 1 to 3 (3:3:2 ratio): aducanumab 1 mg/kg, aducanumab 3 mg/kg, or placebo
- Arms 4 and 5 (3:1 ratio): aducanumab 10 mg/kg or placebo
- Arms 6 and 7 (3:1 ratio): aducanumab 6 mg/kg or placebo
- Arms 8 and 9 (3:1 ratio): aducanumab titrated to 10 mg/kg (1 mg/kg x two doses, 3 mg/kg x four doses, 6 mg/kg x 5 doses, 10 mg/kg thereafter) or placebo

Randomization was stratified by ApoE ϵ 4 status (carrier or noncarrier), with the exception of Arms 8 and 9, which enrolled ApoE ϵ 4 carriers only.

Long Term Extension Period: up to 8 years per protocol

All subjects received aducanumab in this phase, but the dose was blinded. Subjects were eligible for the long-term extension phase if they completed the placebo-controlled portion of the study, received 11 or more doses, did not miss more than 2 consecutive doses, and had a MMSE score >10 at Week 52.

Subjects who had been randomized to aducanumab continued the dose they received in the placebo-controlled phase with the exception of those subjects who were randomized to 1 mg/kg (e.g. Arm 1); they received 3 mg/kg.

Subjects who received placebo during the placebo-controlled phase received aducanumab as follows:

- Arms 3, 5, and 7: aducanumab 6 mg/kg in a titration regimen (2 doses of 3 mg/kg then 6 mg/kg thereafter)
- Arm 9: aducanumab titrated to 10 mg/kg (as above)

Follow-Up Period – a safety follow-up phone call occurred 14 days after the last dose was administered

For this Phase I study, the primary objective was to evaluate the safety and tolerability of multiple doses of aducanumab in subjects with prodromal or mild Alzheimer's disease dementia. Exploratory objectives included several measures of clinical progression, including the CDR scale, MMSE, and others. One of these exploratory efficacy measures included the change in CDR sum of boxes (CDR-SB) score from baseline to Week 54, comparing placebo and aducanumab.

Virgil Tablet

For Protocol 221AD302, ratings for the electronic Clinical Outcome Assessments (eCOAs), including the CDR, were entered into the electronic device, the Virgil Tablet, by the onsite rater. The Virgil Tablet was provided by the vendor, MedAvante.

Briefly, the sequence of events from the start of the assessment to uploading the data into the database included the following:

1. Rater logs onto the tablet and starts the assessment by clicking on "Start". This action generates an Activity Start Date/Time Stamp
2. Rater completes the assessment and clicks on "Submit". This action generates an Activity End Date/Time Stamp
3. The system immediately prompts for an electronic signature of the rater. The rater enters credentials and clicks on "Sign". This action generates a Submission Date/Time Stamp. After the rater clicks on "Sign", no further changes can be made to the data.
4. System immediately queues the assessment for transmission to the Virgil Portal. Audit trails begin once the data has been received on the Virgil Portal.

Of note, if any changes need to be made to the eCOA data after it has been uploaded into the portal, the data is pushed back to the tablet for editing, and these changes are documented in the audit trail.

Data from the Virgil Tablet were reviewed during the clinical investigator inspections to verify CDR scores.

Amyloid-Related Imaging Abnormalities

Amyloid-related imaging abnormalities (ARIA) is an adverse event of special interest for aducanumab. ARIA-E (edema) and ARIA-H (microhemorrhage, superficial siderosis, macro-hemorrhage) are imaging findings identified based on centrally read MRI sequences. The vendor, (b) (4) was responsible for the central reading of the MRIs. All cases of symptomatic ARIA were reported as medically important SAEs, even if none of the other serious criteria were met. All cases of asymptomatic ARIA were recorded as nonserious AEs, unless the clinical investigator considered that the event met SAE criteria.

(b) (4) reported cases of ARIA-E and ARIA-H to both the sponsor and the clinical investigator. All cases were reviewed by the sponsor and clinical investigator, and decisions on dosing continuation, interruption, or discontinuation were based on clinical symptoms and MRI findings.

The clinical investigator inspections evaluated the adverse event reporting for ARIA as well as the processes for maintaining the study blind.

Rationale for Site Selection

The clinical sites were chosen primarily based on risk ranking in the site selection tool, numbers of enrolled subjects, enrollment in both Protocol 221AD103 and Protocol 221AD302, subjects with Amyloid-Related Imaging Abnormalities (ARIA), and prior inspectional history.

III. RESULTS

1. Brian Ott, M.D.

Protocol 221AD103: Site #228
Protocol 221AD302: Site #831
Rhode Island Hospital
593 Eddy Street
Providence, RI 02903
Inspection Dates: 9/8/2020 – 9/14/2020

At this site for Protocol 221AD302, 34 subjects were screened, 17 were randomized, 14 subjects completed the double-blind phase of the study, and 13 subjects continued into the long-term extension phase until the study was terminated by the sponsor. Three subjects discontinued the study during the double-blind phase of the study due to: study termination by the sponsor (n = 2) and withdrawal of consent.

At this site for Protocol 221AD103, 10 subjects were randomized, while 7 subjects completed the double-blind phase of the study and continued into the long-term extension phase. Three subjects discontinued during the double-blind phase of the study due to: study visit burden (n = 2) and adverse event (ARIA-E symptomatic; ARIA-H superficial siderosis, symptomatic; ARIA-H microhemorrhage, symptomatic). Six of the seven subjects discontinued during the long-term extension phase due to: study termination by sponsor (n = 2), progression of disease, death (Subject (b) (6)), adverse event (peripheral edema), and investigator's decision. The narrative of the death was included in the BLA submission with the reported term "Alzheimer's disease progression".

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all randomized subjects in

Protocols 221AD103 and 221AD302 was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, training documents (protocol, raters), IRB/sponsor communications, financial disclosure, test article accountability, inclusion and exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, secondary efficacy endpoint data (Mini Mental Status Examination [MMSE], and primary efficacy endpoint data (Clinical Dementia Rating-Sum of Boxes score [CDR-SB]).

For Protocol 221AD103, all clinical outcome assessments (COAs), including the CDR, were recorded on paper forms. For Protocol 221AD302, all COAs, including the CDR, were entered directly into the Virgil Tablet. For both protocols, the double-blind phase was the focus for the verification of CDR and MMSE scores. The FDA field investigator interviewed the blinded CDR rater who performed ratings for both studies and confirmed that the rater did not have access to any subject-specific study data (e.g. adverse events) that could unblind the rater.

Protocol 221AD103

CDR and MMSE scores for all subjects were verified and one discrepancy was noted. For the CDR assessment at Week 54 of the double-blind phase in Subject (b) (6), the CDR score on one item was changed from 0 to 1 based on a query; however, this data change was not recorded on the paper source.

Protocol 221AD302

CDR and MMSE scores for all subjects were verified.

During review of the Virgil Tablet data, delays in date stamps were noted (see Background). Specifically, for the subjects listed in Table 1, there was a significant delay between the start and end dates for CDR assessments. The CDR rater did not have an explanation for these delays.

Table 1. Virgil Tablets: Delay Between Start and End Dates for CDR Assessments (Protocol 221AD302)

Subject #	Treatment Arm	Visit	Assessment	Start Date of Assessment	End Date of Assessment and Electronic Signature
(b) (6)	Aducanumab high dose	Week 338	CDR	(b) (6)	(b) (6)
	Aducanumab high dose	Week 50	CDR		
	Placebo	Week 338	CDR		

At this site, there was no evidence of underreporting of adverse events.

Reviewer comments: A review of Virgil Tablet date stamps identified delays in the start and end dates of CDR assessments for 3 of 17 (17.6%) subjects participating in Study 221AD302 at this site. Since audit trails began only once data had been uploaded into the Virgil Portal, there is no record for any changes that may have possibly been made to data during these time gaps. However, these CDR assessments occurred at Weeks 50 or Week 338 and not the primary visits of interest for the efficacy analyses (baseline, Week 78). Therefore, the finding is unlikely to have significant impact on trustworthiness and reliability of the primary efficacy data.

Please refer to the Virgil Tablet discussion under the Biogen inspection summary for a more comprehensive discussion.

2. Christopher van Dyck, M.D.

Protocol 221AD103: Site #218

Protocol 221AD302: Site #850

Yale University School of Alzheimer's Disease Research Unit

1 Church Street, 8th Floor

New Haven, CT 06510

Inspection Dates: 9/1/2020 – 9/10/2020

At this site for Protocol 221AD302, 102 subjects were screened, 53 were randomized, 38 subjects completed the double-blind phase of the study, and 36 subjects continued into the long-term extension phase until the study was terminated by the sponsor. Three subjects discontinued the study during the double-blind phase due to: adverse event (asymptomatic ARIA-H microhemorrhage), withdrawal by guardian due to study visit burden, and loss to follow-up. Twelve subjects did not complete the double-blind phase of the study due to study termination by the sponsor.

At this site for Protocol 221AD103, 31 subjects were screened, 13 were randomized, 12 subjects completed the double-blind phase of the study, and 11 subjects continued into the long-term extension phase of the study. One subject discontinued during the double-blind phase of the study due to the adverse event of asymptomatic ARIA-E. All 11 subjects discontinued the study during the long-term extension phase due to: study termination by the sponsor (n = 6), death (Subject (b) (6)), progression of disease, adverse event (atrial fibrillation), and study visit burden (n = 2). The narrative of the death was included in the BLA submission with the reported term "death due to endstage Alzheimer's disease".

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of 7 of 13 (54%) enrolled subjects in Protocol 221AD103 and 8 of 53 (15%) randomized subjects in Protocol 221AD302 was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, training documents (protocol, raters), IRB/sponsor communications, financial disclosure, test article accountability, inclusion and exclusion criteria, adverse event

reports, laboratory results, concomitant medications, protocol deviations, secondary efficacy endpoint data (MMSE), and primary efficacy endpoint data (CDR-SB).

For Protocol 221AD103, COAs, including the CDR, were recorded on paper forms. For Protocol 221AD302, all COAs, including the CDR, were entered directly into the Virgil tablet. For both protocols, the double-blind phase was the focus for the verification of CDR and MMSE scores. CDR and MMSE scores for all subjects reviewed were verified for both protocols.

There were delays in date stamps on the Virgil Tablets used in Protocol 221AD302 (see Background), similar to the findings for Site 831. The CDR rater was interviewed and explained that sometimes she was performing other tasks for other studies and may have forgotten to hit the submit button (which corresponds to the end of the assessment) on the Virgil Tablet.

Table 2. Virgil Tablets: Delay Between Start and End Dates for CDR Assessments (Protocol 221AD302)

Subject #	Treatment Arm	Visit	Assessment	Start Date of Assessment	End Date of Assessment and Electronic Signature
(b) (6)	Placebo	Week 50	CDR	(b) (6)	(b) (6)
		Week 78	CDR		
	Placebo	Week 78	CDR		
	Aducanumab low dose	Week 50	CDR		
	Aducanumab high dose	Week 26	CDR		

There were two adverse events in Subject (b) (6) during the double-blind phase of the study that were not reported to the sponsor. This subject, randomized to aducanumab low dose, experienced a mild headache at the end of the infusion (on (b) (6)) as well as pain in right toe and leg on (b) (6). The duration and outcome of these adverse events is not known.

Reviewer comments: A review of Virgil Tablet date stamps identified delays in the start and end dates of CDR assessments for 4 out of 8 (50%) subjects reviewed during the inspection. Since audit trails began only once data had been uploaded into the Virgil Portal, there is no record for any possible changes that may have been made to data during these time gaps. These CDR assessments occurred at Weeks 26, 50, and 78.

This reviewer reviewed Virgil Tablet date/time stamps for all 53 subjects randomized in Protocol 221AD302 at this site. Based on this review, approximately 20% of all CDR assessments had a >8 hour difference between assessment start and end times.

Please refer to the Virgil Tablet discussion under the Biogen inspection summary for a more comprehensive discussion.

Two unreported adverse events occurring in a single subject for Protocol 221AD302 were noted. It is unlikely that this omission would impact the overall safety analyses

3. Biogen, Inc.

225 Binney Street

Cambridge, MA 02142

Inspection Dates: 10/26/2020 – 11/10/2020

This inspection covered the sponsor practices related to Protocols 221AD103 and 221AD302 and focused on the two clinical investigator sites (above) that had been selected for inspection. Prior to the inspection, information requests were sent to the sponsor requesting the following documents pertaining to Protocol 221AD302: data flow/process maps, data management plans, eCRF audit trails, eCOA audit trails and system logs (Virgil Tablet), and a listing of all inadvertent unblinding incidents. The sponsor responses were being reviewed by this OSI reviewer concurrent with the inspection so that the FDA field investigator could address any questions arising from this review.

Records reviewed during the inspection included, but were not limited to, SOPs, organizational charts, monitoring plan and reports, monitor training records and CVs, vendor contracts, transfer of responsibilities, investigator agreements, financial disclosure forms, pharmacovigilance procedures and records, blinding/unblinding procedures, protocol deviations, adverse event reporting, test article, and Virgil Tablet (validation, user acceptance testing, audit trails).

The futility analysis for Protocols 221AD301 and 221AD302 was conducted by a Quintiles (now IQVIA) unblinded statistician for data collected up to 12/26/2018. This analysis was sent to the Data Monitoring Committee (DMC) on 3/8/2019. The DMC met on 3/11/2019 in a closed session with the statistician who conducted the futility analysis. In a Biogen DMC Data Review Meeting held on 3/19/2019, the DMC recommended study termination. Both protocols were terminated on 3/21/2019. After study termination, the sponsor conducted further blinded analyses on data collected up to the date of study termination. The studies were unblinded on 4/18/2019. On 5/15/2019, the sponsor requested a meeting with the review division. The sponsor met with the review division on 6/14/2019 to discuss the statistical analyses conducted on data collected up to study termination. Further details of this and subsequent meetings with the review division are beyond the scope of this CIS.

Study Unblinding

An Authorization to Release Treatment Assignments for Protocol 221AD302 was signed on 3/21/2019 due to an “urgent need for internal analysis upon the readout of the futility analysis”. Treatment assignment information was released to the Biogen Study Management Team (SMT) statistician. The sponsor released treatment assignments to the IQVIA statistics team on 4/18/2019 (as stated in the Statistical Analysis Plan [SAP] amendment dated 11/4/2019).

In response to a 9/15/2020 FDA information request, the sponsor provided a summary of changes made to eCRFs after April 18, 2019 (date of unblinding) to data collected prior to 3/21/2019 (date of study termination) for Protocol 221AD302. In general, the most common data changes were described as changes to administrative variables. Raw datasets with $\geq 5\%$ changes included End of Study and End of Treatment (Long Term Extension) [DSEOS and DSEOT datasets], Adverse Events [AE dataset], predominantly the end date and outcome of the adverse event [AEENDAT and AEOUT variables], and peripheral blood mononuclear cell (PBMC) sample collection [PBMC dataset].

Changes to the primary efficacy measure, i.e., CDR scores, that were made after April 18, 2019 (date of unblinding) to data collected prior to 3/21/2019 (date of study termination) for Protocol 221AD302 are discussed below under Virgil Tablets.

Reviewer comments: The extent of exploratory analyses beyond those pre-specified in the analysis plan is unknown. The number and extent of changes to eCRFs after April 18, 2019 to data collected prior to March 21, 2019 appear minimal and are unlikely to impact the overall efficacy and safety analyses. Changes to CDR data are discussed below.

Data Integrity - Virgil Tablets

For Protocol 221AD302, the primary efficacy measure, the CDR, was conducted by blinded CDR raters, and data was entered directly into an electronic tablet. The electronic tablet, the Virgil Tablet, was supplied to the sites by the vendor, MedAvante. Audit trails of the Virgil Tablet were requested in the 9/15/2020 information request and were received on 10/6/20 and 10/30/20.

A Virgil Assessment Activity Report was also submitted as requested. This report included several columns with activities and different date/time stamps. Understanding these activities and date/time stamps was important to understand when data could be changed with or without a record of changes appearing in the audit trails (refer to Background section of this report). Briefly, The CDR rater started the assessment by clicking on “Start” and ended the assessment by clicking on “Submit”. The Virgil Tablet then immediately prompted the rater

for an electronic signature which prompted the rater to click on "Sign". After the electronic signature was obtained, the system queued the assessment for transmission to the Virgil Portal. Audit trails began once data was received on the Virgil Portal. If any changes needed to be made to CDR scores after it was uploaded into the portal, the data was pushed back to the tablet for editing and these changes were documented in the audit trail.

The sponsor had requested the Virgil Assessment Activity Report in early 2019, and MedAvante provided the report in April 2019, after the study had been terminated. Virgil tablet audit trails were also reviewed by this reviewer with a focus on any changes to CDR data (for the baseline and Week 78 timepoints) collected prior to 3/20/2019 that were made after the study was unblinded on 4/18/2019.

The following issues were noted during review of the Virgil Assessment Activity Report and the Virgil audit trails:

Delays in Assessment Start and End

In their response, the sponsor noted that 94% of all CDR assessments were completed in less than or equal to four hours. The sponsor noted that for 3.4% of all CDR assessments, there was a delay in completion of the assessment of >8 hours. The sponsor stated that they performed another analysis excluding assessments with a delay in assessment completion >8 hours and that this analysis was consistent with the original analysis results (results of analysis not provided in response). The sponsor did not provide a reason for these time delays.

This reviewer conducted a review of the data for CDR assessments at Week 78 only, for data collected prior to study termination (March 21, 2019), and noted 35/908 (3.8%) subjects with a delay in completion of the CDR assessment >8 hours. For these 35 subjects, the range of delay was 8.2 hours to 35 days, with an average delay of 6.7 days and a median delay of 2 days. The subjects with these delays were approximately equally distributed among the placebo, aducanumab low dose, and aducanumab high dose groups. A review of the date/time stamps noted that these types of delays occurred throughout the entire study, from 2015 to 2019.

This issue was discussed during the inspection of Biogen. The sponsor was not aware of these delays during the conduct of the study as the Virgil Assessment Activity Report was not requested by the sponsor. There did not appear to be any review of data during the study that would have identified these delays and/or institute processes to rectify them, e.g. some alert system that could communicate with the rater, CRO, MedAvante, or sponsor to identify the delays in real time.

Reviewer comments: Since Virgil Tablet audit trails are available only when the data is uploaded to the Virgil Portal, there is no way to know whether any CDR assessments were changed during these delays between assessment start and end.

This reviewer requested that the FDA statistician perform a sensitivity analysis for the 35 subjects with significant delays between the start and end date for the Week 78 CDR assessment to determine the robustness of the reported results. The overall efficacy results were not impacted by exclusion of these 35 subjects.

Delays in Assessment End and Electronic Signature

As noted above, when the rater clicks on "Submit" in the Virgil Tablet, there is an immediate prompt for an electronic signature. According to the sponsor, once the electronic signature is entered, no further changes can be made to the data, and it is in a queue to upload to the Virgil Portal.

This reviewer conducted a review of the data for CDR assessments at Week 78 only, for data collected prior to study termination (March 21, 2019), and found that the average delay between assessment end and electronic signature was 25 seconds. However, it was noted that 66/908 (7.2%) assessments had a delay >1 hour. For these 66 subjects, the range of delay was 1 hour to 381 days, with an average delay of 31.4 days and a median delay of 4.6 days. Only one of these delays was for a Week 78 visit occurring before 3/21/2019 for which the electronic signature date stamp was after the date of unblinding (4/18/2019). Subject (b) (6) randomized to aducanumab low dose, had a Week 78 visit on (b) (6) with the CDR assessment completed on that date but with an electronic signature date stamp on (b) (6) (326 days later). Overall, the subjects with these delays were approximately equally distributed among the placebo, aducanumab low dose, and aducanumab high dose groups.

Reviewer comments: Overall, the average time between the end of a CDR assessment and the electronic signature was 25 seconds, which is consistent with the automated prompt for electronic signature by the Virgil Tablet. The reason for the >1 hour delay in electronic signature in 66/908 (7.2%) of CDR assessments at Week 78 (for data obtained before 3/21/2019) is not known. The delay is significant (>24 hours) for 42 of these 66 subjects.

Per the sponsor, data cannot be changed after the electronic signature is obtained. Therefore, data could still be changed after the assessment was completed and before the electronic signature was obtained, with no record of any changes made. As noted above, Virgil Tablet audit trails are available only when the data is uploaded into the Virgil Portal after the electronic signature is obtained.

This reviewer requested that the FDA statistician perform a sensitivity analysis for the 66 subjects with delays >1 hour between the Week 78 CDR assessment end and electronic signature to determine the robustness of the reported results. The overall efficacy results were not impacted by exclusion of these 66 subjects. Only one of these delays involved an electronic signature obtained after the date of study unblinding. This subject was randomized to aducanumab low dose, which did not demonstrate efficacy.

Delays Between Electronic Signature and Data Upload

In their response, the sponsor noted that there was a delay of >24 hours between the electronic signature and data upload to the Virgil Portal for 4.3% of all CDR assessments.

During the inspection, the sponsor noted that these delays could be due to a number of reasons, including insufficient internet connection at the time of data upload or turning off the Virgil tablet while the data was transferring.

Reviewer comments: The delays between the electronic signature and data upload are less concerning since, according to the sponsor, the data cannot be changed once the electronic signature is obtained.

Maintenance of Study Blind***Clinical Outcome Assessments (COAs)***

Aspects of maintaining the blinding and independence of the COA raters was more detailed for Protocol 221AD302 as it was for Protocol 221AD103, the Phase 1 study. For Protocol 221AD302, raters who performed COAs, including the CDR, were to be independent and not involved in any other aspect of subject care and management. They must have remained blinded to adverse events, concomitant therapy, laboratory data, imaging data, etc. The raters who performed the CDR ratings were to be different from the raters who performed the other COAs (e.g., MMSE, ADAS-Cog13, etc.).

During the two clinical investigator inspections (see above), CDR raters for Protocol 221AD302 were interviewed, and the delegation logs were reviewed. There was no evidence that CDR raters had access to subject-specific data that could unblind them. For Protocol 221AD103, there were four study personnel at Site 218 delegated with performing CDR assessments. Two of these study personnel were also delegated tasks that could potentially unblind them, including “medical assessments (e.g., AE/SAE reporting)” and performing physical examinations. Further discussion of these delegated tasks did not occur during the inspection, and it is not known if these two individuals performed any of the CDR assessments. Upon request, the sponsor provided a list of all CDR raters for all clinical sites. Virgil audit trails were reviewed by this reviewer for 20% of sites, and no CDR scores were found that were entered by study personnel other than these CDR raters.

Changes to the CDR Sum of Boxes Scores

This reviewer conducted a review of the Virgil Tablet audit trails to identify changes to the CDR Sum of Boxes (CDR-SB) Scores made after the date of unblinding (4/18/2019) to data collected prior to study termination (3/21/2019) for the baseline and Week 78 timepoints. CDR-SB score changes were identified in five subjects in the aducanumab low dose group and five subjects in the aducanumab high dose group (no changes were found in the placebo group). All changes were entered by a CDR rater at the site, with the reason specified as “consult with MedAvante.” These data changes were made, on average, approximately 122

days (range 56 to 251 days) after the Week 78 visit in which the CDR assessment was conducted. For the CDR changes for the 5 subjects in the aducanumab low dose group, 2 were decreases in CDR score and 3 were increases in CDR score. For the CDR changes for the 5 subjects in the aducanumab high dose group, 3 were decreases in CDR score and 2 were increases in CDR score. Please see Table 3 below for more details.

Table 3. Changes to CDR-SB Scores for Week 78: Changes Made After Date of Unblinding (4/18/2019) to Data Collected Before Study Termination (3/21/2019)

Subject	Week 78/ET Visit	CDR Sum of Boxes		Date of Change
		Original Score	Changed Score	
Aducanumab Low Dose				
(b) (6) *	(b) (6)	4.5	4	(b) (6)
		5	2.5	
		6	7	
		7	8	
		11	12	
		1.5	3	
Aducanumab High Dose				
(b) (6)	(b) (6)	7.5	5.5	(b) (6)
		2	2.5	
		4.5	5	
		5	7	
		3	2.5	
		7	6	

*CDR scores were changed twice for these subjects

Reviewer comments: Changes to CDR-SB scores for Week 78 that were made after the date of unblinding (4/18/2019) to data collected prior to study termination (3/21/2019) occurred in <1% of subjects. These changes included both increases and decreases in CDR-SB scores in both the aducanumab low and high dose groups. Due to the low number of changes and the lack of a consistent pattern in CDR-SB score changes that would favor aducanumab (i.e., changes to lower CDR-SB scores), it is unlikely that these changes would have an impact on the overall efficacy analyses for the study.

The reason for the data changes was noted as "consult with MedAvante". During the inspection, it was explained that MedAvante reviewed CDR scores which included reviewing audio recordings of the assessments. This might prompt a query to the site to discuss the rating if there were any questions noted upon MedAvante review. If the CDR rater concurred with the suggested change, the data would be sent back to the Virgil Tablet from the Virgil Portal, and the CDR rater would make that change.

Amyloid-Related Imaging Abnormalities (ARIA) and Potential ARIA Unblinding Incidents

ARIA is an adverse event of interest for aducanumab, and cases of Amyloid-Related Imaging Abnormalities-Edema (ARIA-E) as well as Amyloid-Related Imaging Abnormalities-Hemorrhage or superficial siderosis (ARIA-H), both asymptomatic and symptomatic, occurred almost exclusively in subjects receiving aducanumab for both Protocols 221AD103 and 221AD302. Knowledge of ARIA occurring in a specific subject could potentially reveal the study drug assignment for that subject; therefore the blinding for ARIA cases was discussed during the inspection.

For Protocols 221AD103 and 221AD302, MRIs were performed throughout the study to assess cases of ARIA-E or ARIA-H. For Protocol 221AD302, MRIs were performed at screening, Week 14, and every 8 to 12 weeks until the end of the double-blind phase (Week 78). Subjects with ARIA noted on MRI had unscheduled visits for repeat MRIs every 4 weeks until ARIA resolution. MRIs were centrally read by the vendor, (b) (4)

During the inspection, the sponsor explained that the MRI was performed at the local hospital or clinic and that the MRI technician was blinded. The technician removed personally identifiable information (PII) from the image and then sent the MRI to the blinded central reader. The (b) (4) central reader sent their report to the IQVIA Medical Monitor, IQVIA Clinical Research Associate (CRA), and the clinical investigator. The blinded clinical investigator issued the study prescription to the unblinded pharmacist based on the MRI report. The Independent Data Monitoring Committee (IDMC) members also reviewed unblinded data, including cases of ARIA.

As mentioned above, a listing of all potential unblinding events for Protocol 221AD302 was requested as part of an information request. The sponsor's response included, among other things, a listing of incidents of exposure to restricted ARIA-related data. The sponsor noted that special measures and processes to maintain the study blind were implemented to restrict access to ARIA-related data. Subject numbers were therefore not provided in this listing "because they are not collected due to unblinding considerations."

Reviewer comments: Due to the lack of details provided by the sponsor for the potential ARIA unblinding events, the extent of this potential unblinding cannot be determined. Subjects with ARIA, most of whom were randomized to aducanumab, had more frequent MRI scans to assess ARIA resolution. It is possible that the subject and/or caregiver would suspect that the subject was receiving aducanumab if the subject was undergoing frequent (every 4 week) MRI scans. The sample informed consent form provided by the sponsor states that there are 7 visits for brain MRIs, so if subjects underwent more MRI scans, this could potentially unblind them to study treatment. The sample informed consent does provide data regarding the frequency of ARIA in subjects receiving aducanumab (10 – 47% depending on dose) compared to placebo (7%). If subjects were potentially unblinded by the frequency of MRIs, this could bias their reporting to raters for ratings such as the CDR. This potential unblinding issue is beyond the scope of this CIS.

Medicines & Healthcare Products Regulatory Agency (MHRA) Inspection

MHRA conducted a surveillance inspection of Biogen Idec UK Limited, Berkshire, on December 3, 2019 (office-based) and December 10, 2019 – December 13, 2019 (on-site). This inspection covered 5 protocols, one of which was Protocol 221AD301. This inspection did not cover Protocol 221AD302, as this protocol did not enroll any subjects from the United Kingdom.

The review division requested a copy of the MHRA final inspection report from Biogen. The inspection report was finalized by MHRA and received by Biogen on August 21, 2020. Biogen submitted this report to the BLA on August 24, 2020. The review division also requested a copy of Biogen's response to the inspection findings, which Biogen submitted to the BLA on 10/6/2020.

The MHRA inspection report included no critical findings, five major findings, and nine other findings. The five major findings were in five general areas: Essential Documents, Statistics, Data Integrity, Data Integrity Control Processes, and Project Management. Since Protocol 221AD301 and 221AD302 were identical in design and conducted concurrently, inspection findings for Protocol 221AD301 were considered potentially relevant to Protocol 221AD302, the primary efficacy study for this BLA submission. The findings from the MHRA inspection covering Protocol 221AD301 informed FDA's information requests (as outlined above) to the sponsor for Protocol 221AD302.

Complaint

In October 2019, the Office of Scientific Investigations (OSI) received a complaint (C # (b) (4)) alleging that (b) (4). The complainant specifically mentioned Protocols 221AD301 and 221AD302 in this complaint but acknowledged that this (b) (4) was involved with multiple (b) (4) across many sponsors. During the Biogen inspection, the FDA field investigator found no evidence that (b) (4) was used (b) (4) for either of the protocols mentioned in the complaint. The sponsor had also denied involvement of (b) (4) for these protocols when asked by the review division. The FDA field investigator noted that (b) (4) for the Phase 1 study, 221AD103. Due to time constraints, lack of involvement of (b) (4) in the pivotal clinical trial, and limitations of following up on the specifics of the complaint due to the inability of FDA to conduct inspections (b) (4) this complaint was not further addressed during the Biogen inspection.

{See appended electronic signature page}

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 10, 2020
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	BLA 761178
Product Name and Strength:	Aduhelm (aducanumab-avwa) Injection, 170 mg/1.7 mL (100 mg/mL) and 300 mg/3 mL (100 mg/mL)
Applicant/Sponsor Name:	Biogen Inc. (Biogen)
OSE RCM #:	2020-1503-1
DMEPA Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted information to clarify the expiration date format (see Appendix A) received on October 9, 2020 and revised container labels and carton labeling (Appendix B) received on October 30, 2020 for Aduhelm. The Division of Neurology 1 (DN 1) requested that we review the revised carton labeling and container labels for Aduhelm to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Weitzman B. Label and Labeling Review for Aduhelm (BLA 761178). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 03. RCM No.: 2020-1503.

APPENDIX A. APPLICANT'S RESPONSE TO THE AGENCY'S OCTOBER 3, 2020 COMMENTS
RECEIVED ON OCTOBER 9, 2020.

Available in docuBridge via: <\\CDSESUB1\evsprod\bla761178\0039\m1\us\multiple-module-info-carton-container-label.pdf>

Agency's Comment:

Clarify whether you intend to use numerical or alphabetical characters to denote the month in your proposed expiration date format.

Applicant Response:

Biogen has updated the expiration date to YYYY-MM which is intended to be numerical characters.

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/s/

BEVERLY WEITZMAN
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 3, 2020
Requesting Office or Division:	Division of Neurology 1 (DN1)
Application Type and Number:	BLA 761178
Product Name and Strength:	Aduhelm (aducanumab-avwa) Injection, 170 mg/1.7 mL (100 mg/mL) and 300 mg/3 mL (100 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Biogen Inc. (Biogen)
FDA Received Date:	July 7, 2020
OSE RCM #:	2020-1503
DMEPA Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 REASON FOR REVIEW

As part of the approval process for Aduhelm (aducanumab-avwa) Injection, the Division of Neurology 1 (DN1) requested that we review the proposed Aduhelm prescribing information (PI), medication guide (MG), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Information Request	E
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information (PI) – General Issues			
1.	The PI contains discrepancies in terms of the intend to market strengths. We acknowledge that the Applicant plans on marketing only the 170 mg/1.7 mL and 300 mg/3mL product strengths.	In response to our September 1, 2020 Information Request, the Applicant states they intend to market only the 170 mg/1.7 mL (100 mg/mL) and 300 mg/3 mL (100 mg/mL) product strengths. However, the PI has not been revised to reflect this.	Revise to include only the intend-to-market strengths throughout the PI labeling.

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The nonproprietary name suffix placeholder "xxxx" is used throughout the PI labeling.	The nonproprietary name suffix "avwa" was found to be conditionally acceptable on September 11, 2020. ^a	Replace the placeholder 'xxxx' with the conditionally acceptable nonproprietary name suffix "avwa" (i.e., aducanumab-avwa) throughout the PI.
Highlights of Prescribing Information (HPI)			
1.	The administration technique "via an in-line filter during infusion" is not included the Dosage and Administration section of the HPI.	Inclusion of instruction to use an "in-line filter during infusion" may help mitigate the risk for wrong technique medication errors.	We recommend adding a new bullet point to ensure that the correct administration technique is stated. For example, <ul style="list-style-type: none"> • Administer as an intravenous infusion over approximately one hour via a 0.2 or 0.22 micron in-line filter.
2.	The following statement in the Dosage and Administration section of the HPI: (b) (4) is incomplete and can be improved to emphasize correct preparation.	To emphasize the correct preparation and help avoid errors associated with using a wrong solution for dilution.	Revise the statement "(b) (4)" to read "Dilution in 100 mL of 0.9% Sodium Chloride Injection USP, is required prior to administration (2.5, 2.6)".
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The infusion instructions for treatment initiation do not include the infusion time.	To increase clarity and prevent incorrect infusion time during treatment initiation.	Ensure the dosing instructions for treatment initiation include the infusion time.
2.	Section 2.5 of the PI includes the statement: (b) (4)	(b) (4)	Revise the statement "(b) (4)" to (b) (4)

^a Mena-Grillasca, C. Nonproprietary Name Suffix Review (BLA 761178). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 SEP 11. Panorama No. 2020-1645.

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4)	(b) (4) See Guidance for Industry: <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> . Food and Drug Administration. 2013. (Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf)	read "Select the correct vial(s) for the required volume."
Full Prescribing Information – Section 2 Dosage and Administration and Section 16 How Supplied/Storage and Handling			
1.	As currently presented in Section 2.5 and 16.2 of the PI, the following storage statement for "after dilution" is confusing and unclear: (b) (4)	The meaning of the storage statement for after dilution (b) (4) could be misinterpreted and poses risk of improper storage. For example, the following interpretations may be possible: (b) (4)	We recommend the storage instructions for "after dilution" be revised for clarity to mitigate possible storage errors. For example, consider revising to state: "...for up to a maximum of 84 hours as follows: Up to 72 hours at 2°C to 8°C (36°F to 46°F), followed by Up to 12 hours at 30°C (86°F).
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	Section 16.1 may need to be revised once the	Post-Market experience indicates that similarity of	We recommend the NDC product code be revised to

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Sponsor determines how to differentiate the NDC product codes. Currently the middle digits of the NDC product codes are sequential (i.e., 101 and 102) which is not an effective differentiating feature.	the NDC product code numbers has led to selecting and dispensing of the wrong strength.	ensure consistency with the below container label and carton labeling recommendations, if appropriate. See Table 3 recommendation number five below under the heading "Container Labels and Carton Labeling".
2.	In Section 16.2 the temperature statements do not contain the temperature scale designation (i.e., °C and °F) after the numerical value.	We are concerned that this information could be misinterpreted and may pose a risk of drug degradation.	We recommend that the degree symbol and temperature scale follow each numeric value denoting temperature ranges, e.g., revise "36-46°F" to read "36°F to 46°F" to increase clarity.

Table 3. Identified Issues and Recommendations for Biogen Inc. (Biogen) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Recommendation (Container Labels and Carton Labeling)			
1.	The color scheme of the 300 mg/3 mL strength, the proprietary name and top flap of the carton labeling appear in a similar blue color.	The use of similar blue colors for the proprietary name, top flap of the carton labeling and one of the product's strengths minimizes the difference between the two strengths and may lead to wrong strength selection errors.	Revise the font color of the proprietary name and top flap of the carton labeling or the color utilized for the 300 mg/3 mL strength to appear in its own unique color and ensure the color does not overlap with any other colors utilized in highlighting the strengths.
Container Labels and Carton Labeling			
1.	The labels and labeling contain the nonproprietary name suffix placeholder "xxxx."	The nonproprietary name suffix "avwa" was found to be conditionally acceptable on September 11, 2020.	Replace the placeholder 'xxxx' with the conditionally acceptable nonproprietary name suffix "avwa" (i.e., aducanumab-avwa) on the

Table 3. Identified Issues and Recommendations for Biogen Inc. (Biogen) (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			container labels and carton labeling.
2.	The color contrast of the (b) (4) text (i.e., active ingredient and dosage form) against the white background appears difficult to read.	Insufficient color contrast may make text difficult to read. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. (Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf)	Increase the prominence of the active ingredient and dosage form taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
3.	As currently presented, the proper name is not enclosed in parentheses.	This layout is not consistent with the presentation for Specified Biologics per 21 CFR 201.10 (g)(2).	Enclose the proper name in parentheses. For example: Aduhelm (aducanumab-avwa) Injection
4.	The total concentration and concentration per mL are presented on the same line, which may hinder readability.	The presentation of the total concentration (i.e., 170 mg/1.7 mL and 300 mg/3 mL) and concentration per mL (100 mg/mL) can be improved.	To improve readability of the concentration statements, if space allows, consider presenting the total concentration and concentration per mL on two lines. For example, (170 mg/1.7 mL represented): 170 mg/1.7 mL (100 mg/mL)
5.	As currently presented, the NDC product code numbers (middle 3 digits) are sequential (i.e., -101- for 170	The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation.	Revise the product code in the NDC numbers to ensure that the middle three digits (XXX) are not sequential between the 170 mg/1.7 mL and 300

Table 3. Identified Issues and Recommendations for Biogen Inc. (Biogen) (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	mg/1.7 mL and -102- for 300 mg/3 mL)	The similarity of the product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature.	mg/3 mL product strengths. If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type. For example: XXXX- XXX -XX.
Container Labels			
1.	The proposed format for the expiration date (that is, MM/YYYY) does not specify whether the month (that is, MM) will be displayed using numerical (for example, 06), or alphabetical (for example, JU) characters.	We are unable to assess the expiration date format from a medication safety perspective (for example, may increase the risk for deteriorated drug medication errors).	Clarify whether you intend to use numerical or alphabetical characters to denote the month in your proposed expiration date format. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a

Table 3. Identified Issues and Recommendations for Biogen Inc. (Biogen) (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			hyphen or a space be used to separate the portions of the expiration date.
2.	It is unclear whether the linear barcode on the label and labeling contains, at a minimum, the appropriate National Drug Code (NDC) number.	The NDC number must be contained within the linear barcode per 21 CFR 201.25.	Ensure the linear barcode on the container label and carton labeling contains, at a minimum, the NDC number in accordance with 21 CFR 201.25.
Carton Labeling			
1.	The format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

Table 3. Identified Issues and Recommendations for Biogen Inc. (Biogen) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The dosage statement can be improved.	To ensure consistency with the physician labeling rule (PLR) formatted Prescribing Information.	Revise the statement, (b) (4) to read "Dosage: See prescribing information."
3.	The carton labeling instructs (b) (4) which is not specified on the carton labeling.	To emphasize the correct preparation and help avoid errors associated with using a wrong solution for dilution.	We recommend adding the statement "Must be diluted with 100 mL of 0.9% Sodium Chloride Injection, USP prior to use" on the side panel of the carton labeling.
4.	The discard statement is not prominently visible on the carton labeling.	The discard statement "discard unused portion" may be overlooked.	We recommend adding the statement "Discard unused portion" to the top flap of the carton labeling to minimize the risk of the entire contents of the vial being given as a single dose.
5.	The carton labeling can be improved to align with the administration technique "use an in-line filter during infusion".	Inclusion of instruction to "use an in-line filter during infusion" on the carton labeling may help mitigate the risk for wrong technique medication errors.	We recommend adding the statement "Use a 0.2 or 0.22 micron in-line filter during infusion" to the side or back panel of the carton labeling.
6.	As currently presented the storage statement lacks prominence.	Lack of prominence of the storage statement may increase the risk of the storage information being overlooked. If the storage information is overlooked this could lead to degradation of the product due to improper storage.	We recommend bolding the statement "Refrigerate at 2°C to 8°C (36°F to 46°F)" to increase the prominence and minimize the risk of the storage statement being overlooked.

4 CONCLUSION

Our evaluation of the proposed Aduhelm prescribing information (PI), container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Biogen Inc. (Biogen) so that recommendations are implemented prior to approval of this BLA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Aduhelm that Biogen Inc. (Biogen) submitted on July 7, 2020.

Table 4. Relevant Product Information for Aduhelm	
Initial Approval Date	N/A
Active Ingredient	aducanumab
Indication	Delay clinical decline in patients with Alzheimer's disease
Route of Administration	Intravenous infusion
Dosage Form	Injection
Strength	170 mg/1.7 mL (100 mg/mL) and 300 mg/3 mL (100 mg/mL)
Dose and Frequency	<ul style="list-style-type: none"> Initiation: 1 mg/kg for 2 doses, 3 mg/kg for 2 doses, 6 mg/kg for 2 doses administered every 4 weeks Maintenance: 10 mg/kg every 4 weeks
How Supplied	Single dose vials
Storage	<p><u>Unopened vial:</u> Store in original carton until use. Store in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Protect from light. If no refrigeration is available, ADUHELM may be stored unopened in its original carton, protected from light (b) (4) 25°C (77°F) for up to 3 days. Prior to dilution, unopened vials of ADUHELM (b) (4) be removed from and returned to the refrigerator if necessary. Total combined time out of refrigeration and exposure to light should not exceed 24 hours at room temperature.</p> <p><u>Diluted solution:</u> After dilution, immediate use is recommended. If not administered immediately, store the (b) (4) solution of ADUHELM in 0.9% Sodium Chloride Injection, USP for up to 3 days at 2-8°C (36-46°F) (b) (4) 12 hours at 30°C (86°F).</p>
Container Closure	<p>(b) (4) clear glass vials with (b) (4) rubber stopper (b) (4)</p> <p>The stoppered vial is sealed with an aluminum closure with a flip-off button.</p>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 1, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Aduhelm, aducanumab, and BLA 761178. Our search identified zero previous relevant reviews.

APPENDIX E. INFORMATION REQUEST

E.1 Information Request

During our review of the label and labeling we identified a discrepancy regarding the proposed strengths listed in Section 3 'Dosage Forms and Strengths' compared to Section 16.1 'How Supplied' of the prescribing information (PI) and the container labels and carton labeling. On September 1, 2020, we sent an Information Request to Biogen to clarify which strengths the Applicant intends to market.

IR available in DARRTS

via: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805907fb>

E.2 Response

The Applicant responded to DMEPA's IR on September 1, 2020. In their response, Biogen stated that they intend to market only the following strengths:

- 170 mg/1.7 mL (100 mg/mL)
- 300 mg/3 mL (100 mg/mL)

Response available in docuBridge via:

<\\CDSESUB1\evsprod\bla761178\0021\m1\us\cover-letter-20200901.pdf>

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Aduhelm labels and labeling submitted on July 7, 2020 by Biogen Inc. (Biogen).

- Container labels: 170 mg/1.7 mL (100 mg/mL) and 300 mg/3 mL (100 mg/mL)
- Carton labeling: 170 mg/1.7 mL (100 mg/mL) and 300 mg/3 mL (100 mg/mL)
- Medication Guide (image not shown)
Refer to link in docuBridge for Medication Guide:
<\\CDSESUB1\evsprod\bla761178\0003\m1\us\draft-labeling-mg-20200624.pdf>
- Prescribing Information (Image not shown)
Refer to link in docuBridge for Prescribing Information:
<\\CDSESUB1\evsprod\bla761178\0003\m1\us\annotated-draft-labeling-uspi-20200603.pdf>

^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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